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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

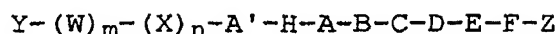
(51) International Patent Classification ⁵ : C07K 7/08, 7/02, 5/02 A61K 37/02	A1	(11) International Publication Number: WO 93/00359 (43) International Publication Date: 7 January 1993 (07.01.93)
(21) International Application Number: PCT/US92/04968 (22) International Filing Date: 18 June 1992 (18.06.92) (30) Priority data: 723,616 27 June 1991 (27.06.91) US (71) Applicant: THE DU PONT MERCK PHARMACEUTICAL COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US). (72) Inventors: ARVANTIS, Argyrios ; 101 Willow Glen, Kennett Square, PA 19348 (US). CAIN, Gary, Avonn ; 8 Wayne Drive, Wilmington, DE 19809 (US). CHRISTOS, Thomas, Eugene ; 3757 Barnsley Chrome Road, Oxford, PA 19363 (US). CONFALONE, Pasquale, Nicholas ; 722 Hertford Road, Wilmington, DE 19803 (US). POT-TORF, Richard, Scott ; 12 Glenbarry Drive, Wilmington, DE 19808 (US). SCHMIDT, William, Koch ; 1 Bridleshire Circle, Newark, DE 19711 (US).		(74) Agents: FERGUSON, Blair, Q. et al. ; The Du Pont Merck Pharmaceutical Company, Legal/Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US). (81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: MODIFIED PEPTIDES TRANSPORTABLE INTO THE CENTRAL NERVOUS SYSTEM (57) Abstract This concerns modified peptides and their pharmaceutically acceptable salts which can effectively penetrate the blood-brain barrier. Also of concern are pharmaceutical compositions containing these peptides and methods of treatment using such compositions.		

CLAIMS

What is claimed is:

1. A compound of the formula

5



wherein

- Y is a lipophilic moiety having the structure
- 10 L-C(O)-, or R-(CH₂)_p-C(O)-(CH₂)_r-, provided that when Y is L-C(O)- then L is selected from the group consisting of (i) at least one alkyl group having 1-16 carbon atoms, said alkyl group can be branched or unbranched, unsubstituted or substituted with at least one cyclic
- 15 moiety selected from the group consisting of a cycloalkyl group having 3-8 carbon atoms, a heterocyclic group having 5-7 atoms in which the heteroatom is N, O, or S, or an aryl group having 6-15 carbon atoms wherein said aryl group can be unsubstituted or substituted with
- 20 at least one alkyl group having 1-4 carbon atoms, (ii) perfluoroalkyl having 1-10 carbon atoms which can be unsubstituted or substituted with at least one cyclic group selected from the group consisting of an aryl group having 6-10 carbon atoms, a cycloalkyl group
- 25 having 3-8 carbon atoms, or a heterocyclic group having 5-7 atoms in which the heteroatom is N, O, or S, (iii) cycloalkyl having 3-8 carbon atoms, (iv) bicycloalkyl having 6-18 carbon atoms, (v) tricycloalkyl having 6-18 carbon atoms, (vi) R¹-NH-R² wherein R¹ is H or alkyl
- 30 having 1-4 carbon atoms; R² is selected from the group consisting of alkanediyl, branched or unbranched, having 1-16 carbon atoms, unsubstituted or substituted with at least one cyclic group selected from the group consisting of cycloalkyl having 3-8 carbon atoms,
- 35 heterocyclic having 5-7 atoms in which the heteroatom is

N, O, or S, or an aryl group having 6-15 carbon atoms unsubstituted or substituted with at least one alkyl group having 1-4 carbon atoms, alkylcycloalkyl branched or unbranched having 4-16 carbon atoms wherein the
5 cycloalkyl group has 3-8 carbon atoms, cycloalkylalkyl branched or unbranched having 4-16 carbon atoms wherein the cycloalkyl group has 3-8 carbon atoms, alkylaryl substituted with at least one moiety selected from the group consisting of alkyl, branched or unbranched,
10 having 7-16 carbon atoms, said alkyl group being unsubstituted or substituted with NHR^1 or OH, said aryl group being unsubstituted or substituted with at least one alkyl group having 1-4 carbon atoms, arylalkyl substituted with at least one moiety selected from the
15 group consisting of alkyl, branched or unbranched, having 7-16 carbon atoms, said alkyl group being unsubstituted or substituted with NHR^1 or OH, said aryl group being unsubstituted or substituted with at least one alkyl group having 1-4 carbon atoms, or
20 alkylheterocyclic substituted with an alkyl group, branched or unbranched, having 6-16 carbon atoms, said heterocyclic having 5-7 atoms in which the heteroatom is N, O, or S,

further provided that when Y is $\text{R}-(\text{CH}_2)_p-\text{C}(\text{O})-(\text{CH}_2)_r-$ then R is a cyclic group selected from the group
25 consisting of cycloalkyl having 3-8 carbon atoms, heterocyclic having 5-7 atoms in which the heteroatom is N, O, S, or heterocyclic having 5-7 atoms in which the heteroatom is N and said heterocycle has at least one
30 carbonyl moiety adjacent to the heteroatom, or aryl having 6-15 carbon atoms unsubstituted or substituted with at least one alkyl group having 1-4 carbon atoms; p and r are independently integers from 0 to 6;

W is an amino acid residue selected from the group
35 consisting of arginine, lysine, ornithine, homoarginine,

2,4-diaminobutyric acid, 2,3-diaminopropionic acid, norleucine, N-methylnorleucine, D-arginine, D-lysine, proline, and 4-aminocyclohexylalanine.

5 X is an amino acid residue selected from the group consisting of arginine, lysine, ornithine, homoarginine, 2,4-diaminobutyric acid, 2,3-diaminopropionic acid, norleucine, N-methylnorleucine, D-arginine, D-lysine, proline, 4-aminocyclohexylalanine, alanine, or an alpha-amino acid residue substituted at the alpha carbon with
10 at least one alkyl group having 1-6 carbon atoms, or said alpha-carbon atom is part of a cyclic moiety selected from the group consisting of cycloalkyl having 3-8 carbon atoms or heterocyclic having 3-8 atoms in which the heteroatom is N, O, or S;

15 m and n are independently 0 or 1, provided that m and n are not both 0 unless L is R^1-NH-R^2 ;

A', A, C, and E are independently selected from the group consisting of -CONH-, -CON(CH₃)-, -N(CH₃)CO-, -NHCR'R"-, -CR'R"NH-, -SO₂NR'R"-, -NR'R"SO₂-, -CH₂NH-,
20 -CH₂O-, -CH₂S-, -NHCH₂-, -OCH₂-, -CSNH-, -NHCONH-, -S(O)CH₂-, -S(O)₂CH₂-, -NHSC-, -CH₂S(O)-, -CH₂S(O)₂-, -SCH₂-, cis- or trans- -CH=CH-, -NHCO-, -CH₂CH₂-, -CF₂CF₂-, -CF=CF-, -CF=CH-, -CH=CF-, -COCH₂-, -CH₂CO-, -CH(OH)CH₂-, -CH₂CH(OH)-, 1,2-cyclopropyldiyl, and
25 4,5-tetrazolyldiyl, wherein R' and R'' are independently lower alkyl groups having 1-6 carbon atoms;

H is an amino acid residue selected from the group consisting of proline or N-methylaminobutyric acid;

30 B is an amino acid residue selected from the group consisting of tyrosine, phenylalanine, tryptophan, naphthylalanine, phenylglycine, and beta-phenylproline;

D is an amino acid residue selected from the group consisting of isoleucine, leucine, tert-leucine, and phenylglycine;

F is an amino acid residue selected from the group consisting of leucine, valine, and methionine; and

Z is OH or OR³ wherein R³ is an alkyl group having 1-6 carbon atoms.

- 5 2. A compound according to claim 1 wherein Y is a lipophilic moiety having the structure L-C(O)- or R-(CH₂)_p-C(O)-(CH₂)_r-, provided that when Y is L-C(O)- then L is selected from the group consisting of (i) alkyl, branched or unbranched, having 1-16 carbon atoms, (ii) 10 perfluoroalkyl having 1-10 carbon atoms, (iii) cycloalkyl having 3-8 carbon atoms, (iv) bicycloalkyl having 6-18 carbon atoms, (v) tricycloalkyl having 6-18 carbon atoms, (vi) R¹-NH-R²- wherein R¹ is H or alkyl having 1-4 carbon atoms, R² is selected from the group 15 consisting of alkanediyl, branched or unbranched having 1-16 carbon atoms, alkylaryl substituted with at least one moiety selected from the group consisting of alkyl, branched or unbranched, having 7-16 carbon atoms, said alkyl group being unsubstituted or substituted with NHR¹ 20 or OH, said aryl group being unsubstituted or substituted with at least alkyl group having 1-4 carbon atoms, or arylalkyl substituted with at least one moiety selected from the group consisting of alkyl, branched or unbranched, having 7-16 carbon atoms, said alkyl group 25 being unsubstituted or substituted with NHR¹ or OH, said aryl group being unsubstituted or substituted with at least one alkyl group having 1-4 carbon atoms;
- further provided that when Y is R-(CH₂)_p-C(O)-(CH₂)_r- then R is a cyclic group selected from the group 30 consisting of cycloalkyl having 3-8 carbon atoms, aryl having 6-15 carbon atoms unsubstituted or substituted with at least one alkyl group having 1-4 carbon atoms, heterocyclic having 5-7 atoms in which the heteroatom is N, O, or S, or heterocyclic having 5-7 atoms in which 35 the heteroatom is N and said heterocycle has at least

one carbonyl moiety adjacent to the heteroatom; p and r are independently integers from 0 to 6;

W is an amino acid residue selected from the group consisting of arginine, lysine, ornithine, 2,4-diaminobutyric acid, norleucine, N-methylnorleucine, D-arginine, 4-aminocyclohexylalanine, or proline;

X is an amino acid residue selected from the group consisting of arginine, lysine, ornithine, 2,4-diaminobutyric acid, norleucine, N-methylnorleucine, D-arginine, proline, 4-aminocyclohexylalanine, alanine, or an alpha-amino acid residue in which the alpha carbon is part of cyclic moiety selected from the group consisting of cycloalkyl having 3-8 carbon atoms or heterocyclic having 3-8 atoms in which the heteroatom is N, O, or S;

m and n are independently 0 or 1, provided that m and n are not both 0 unless L is R^1-NH-R^2- ;

A', A, C, and E are independently selected from the group consisting of $-CONH-$, $-CH_2NH-$, $-CH_2O-$, $-CH_2S-$, $-NHCH_2-$, $-OCH_2-$, $-CSNH-$, $-NHSC-$, $-SCH_2-$, cis- or trans- $-CH=CH-$, $-NHCO-$, $-CH_2CH_2-$, $-CF_2CF_2-$, $-CF=CF-$, $-CF=CH-$, $-CH=CF-$, $-COCH_2-$, $-CH_2CO-$, $-CH(OH)CH_2-$, $-CH_2CH(OH)-$;

H is an amino acid residue selected from the group consisting of proline or N-methylaminobutyric acid;

B is an amino acid residue selected from the group consisting of tyrosine, phenylalanine, tryptophan, naphthylalanine, phenylglycine, and beta-phenylproline;

D is an amino acid residue selected from the group consisting of isoleucine, leucine, tert-leucine, and phenylglycine;

F is an amino acid residue selected from the group consisting of leucine, valine, and methionine; and

Z is OH or OR^3 wherein R^3 is alkyl having 1-6 carbon atoms.

3. A compound according to claim 1 wherein

Y is selected from the group consisting of acetyl, pivaloyl, neopentylcarbonyl, n-perfluorooctanoyl, 1-bicyclo[3.3.0]octanecarbonyl, 2-bicyclo[2.2.1]heptane-acetyl, 1-adamantanecarbonyl, 2-pyrrolidinecarbonyl
5 (prolyl), 2-(5-pyrrolid-5-one)-carbonyl[pyroglutamyl], benzoyl, 4-tert-butylbenzoyl, 4-phenylbenzoyl, nicotinoyl, 2-benzyl-5-aminopentanoyl, trans-4-(aminomethyl)-cyclohexanecarbonyl, 2-(aminomethyl)-benzoyl, and 4-(aminocyclohexyl)-alanyl;

10 W is an arginine residue;

X is an amino acid residue selected from the group consisting of arginine, lysine, ornithine, 4-aminocyclohexylalanine, 4-aminopiperidine-4-carboxylic acid, 1-aminocyclopentanecarboxylic acid, 1-
15 aminocyclobutanecarboxylic acid, or 1-aminocyclopropanecarboxylic acid;

m and n are independently 0 or 1, provided that m and n are not both zero, except when Y is 2-benzyl-5-aminopentanoyl then m and n can be zero, and further
20 provided that when Y is acetyl then m and n are 1;

A', C, and E are -CONH-;

A is -CONH- or -CH₂NH-;

H is a proline residue;

B is an amino acid residue selected from the group
25 consisting of tyrosine and tryptophan;

D is an amino acid residue selected from the group consisting of isoleucine, tert-leucine, and phenylglycine;

F is a leucine residue;

30 Z is OH or OCH₃.

4. A compound according to claim 1 wherein

Y is selected from the group consisting of 1-adamantanecarbonyl, 2-benzyl-5-aminopentanoyl, benzoyl, nicotinoyl, and acetyl;

35 W is an arginine residue;

X is an amino acid residue selected from the group consisting of arginine, lysine, and ornithine;

m and n are independently 0 or 1, provided that m and n are not both zero, except when Y is 1-benzyl-5-aminopentanoyl then m and n can be zero, and further provided that when Y is acetyl, both m and n are 1;

A', A, C, and E are -CONH-;

H is a proline residue;

B is an amino acid residue selected from the group consisting of tyrosine and tryptophan;

D is an amino acid residue selected from the group consisting of isoleucine, tert-leucine, and phenylglycine;

F is a leucine residue;

Z is OH or OCH₃.

5. A compound according to claim 1 wherein

Y is selected from the group consisting of 1-adamantanecarbonyl, 2-norbornaneacetyl, 1-perfluorooctanoyl;

W is an amino acid residue selected from the group consisting of Arg, Lys, Orn;

X is an amino acid residue selected from the group consisting of Arg, Lys, Orn, 1-aminocyclopentane-1-carbonyl, 2-, 3-, or 4-amino-piperidine-2-, 3-, or 4-carbonyl;

m and n are independently 0 or 1 provided that m and n are not both 0;

A, C, and E are independently -CO-NH-, -CH₂NH-, or trans-CH=CH;

B is an amino acid residue selected from the group consisting of Tyr, Phe, Trp;

D is amino acid residue selected from the group consisting of Ile, Leu, Pgl, Gly;

F is an amino acid residue selected from the group consisting of Leu, Val; and

Z is OH or OCH₃.

6. A compound according to claim 1 wherein

Y is 1-adamantanecarbonyl;

W and X are independently Arg or Lys;

5 m and n are independently 0 or 1 provided that m and n are not both 0;

A, C and E are independently -CONH-, -CH₂NH-, or trans-CH=CH-;

B is Tyr;

10 D is Ile;

F is Leu; and

Z is OH or OCH₃.

7. A compound according to claim 1 which is

selected from the group consisting of:

15 N^α-(1-adamantanecarbonyl)-Arg-Pro-Tyr-Ile-Leu;

N^α-(1-adamantanecarbonyl)-Arg-Arg-Pro-Tyr-Ile-Leu;

N^α-(1-adamantanecarbonyl)-Lys-Pro-Tyr-Ile-Leu;

N^α-(1-adamantanecarbonyl)-Lys-Pro-Ψ[CH₂NH]-Tyr-Ile-Leu;

N^α-(1-adamantanecarbonyl)-Lys-Pro-Ψ[CH=CH]-Tyr-Ile-Leu;

20 N^α-(cis-bicyclo(3.3.0)octane-2-carbonyl)-Lys-Pro-Tyr-Ile-Leu;

N^α-(1-adamantanecarbonyl)-Orn-Pro-Tyr-Ile-Leu;

N^α-(1-adamantanecarbonyl)-Lys-Pro-Trp-Ile-Leu;

N^α-(1-adamantanecarbonyl)-Lys-Pro-Tyr-(S)-2-

25 phenylglycyl-Leu;

N^α-(2-norbornaneacetyl)-Lys-Pro-Tyr-Ile-Leu;

N^α-(CF₃(CF₂)₆CO)-Lys-Pro-Tyr-Ile-Leu;

4-(1'-adamantanecarbamido)-4-piperidine-carbonyl-Pro-Tyr-Ile-Leu;

30 N^α-(1-adamantanecarbonyl) Lys-Pro-Tyr-Ile-Leu (OMe);

N^α-(nicotinoyl) Lys-Pro-Tyr-Ile-Leu;

N^α-(Boc)Orn-Pro-Ψ[CH₂NH]Tyr-Ile-Leu;

N^α-(Boc)Orn-Pro-TyrΨ[CH₂NH]-Ile-Leu;

N^α-(Boc)Orn-Pro-TyrΨ[CH=CH]-Ile-Leu;

35 N^α-(Boc)Orn-Pro-Ψ[CH=CH]-Tyr-Ile-Leu;

N^{α} -(PhCO)-Lys-Pro-Tyr-Ile-Leu;

N^{α} (t-BuCO)-Lys-Pro-Tyr-Ile-Leu;

N^{α} -(t-BuCH₂CO)-Lys-Pro-Tyr-Ile-Leu;

N^{α} -(4-Ph-C₆H₄-CO)-Lys-Pro-Tyr-Ile-Leu;

5 N^{α} -(4-t-Bu-C₆H₄-CO)-Lys-Pro-Tyr-Ile-Leu;

N-(2-benzyl-5-aminopentanoyl)-Pro-Tyr-Ile-Leu;

N^{α} -(1-adamantanecarbonyl)-Arg-Arg-Pro-Tyr-Tle-Leu;

N^{α} -acetyl-Arg-Arg-Pro-Tyr-S-2-phenylglycyl-Leu; or

N^{α} -(1-adamantanecarbonyl)-Lys-Pro-Tyr-Tle-Leu.

10 8. A pharmaceutical composition comprising a suitable pharmaceutical carrier and an antipsychotic amount of a compound of claims 1-7.

 9. A method of treating psychosis in a mammal which comprises administering to the mammal an
15 antipsychotic effective amount of a compound of claims 1-7.

 10. A method of treating pain in a mammal which comprises administering to the mammal an analgesic effective amount of a compound of claims 1-7.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/04968

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07K7/08;	C07K7/02;	C07K5/02; A61K37/02
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07K ; A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 333 071 (EISAI CO.) 20 September 1989 cited in the application see the whole document	1-10
X	US,A,4 425 269 (CHRISTY ET AL.) 10 January 1984 cited in the application see examples 1-7	1-10
<p>¹⁰ Special categories of cited documents : ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
07 OCTOBER 1992		02. 11. 92
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer P. Masturzo Il Pro Per Turco

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	<p>BIOCHEMICAL PHARMACOLOGY vol. 36, no. 6, 1987, GB pages 869 - 874 K S KANBA ET AL. 'comparison of the stimulation of inositol phospholipid hydrolysis and of cGMP formation by neurotensin, some of its analogs and neuromedin N in neuroblastoma clone NIE-115' see table 1</p> <p style="text-align: center;">---</p>	1-10
P,X	<p>203RD ACS NAT. MEETING, S. FRANCISCO, CALIFORNIA, APRIL 5-10, 1992, ABSTRACT PAPERS: ABSTRACT NO. 84 vol. 203, no. 1-3, G A CAIN ET AL. 'neurotensin based analgesic identification of minimally active fragment : enhancement of potency, duration of action, and transport properties' see the whole document</p> <p style="text-align: center;">---</p>	1-10
P,X	<p>203RD ACS NAT. MEETING, S. FRANCISCO, CALIFORNIA, APRIL 5-10, 1992, ABSTRACT PAPERS, ABSTRACT NO 81 vol. 203, no. 1-3, W K SCHMIDT ET AL. 'adamantoyl-lys-pro-tyr-ile-leu, ada-kypil, a systematically active neurotensin 9-13 analog with ana analgetic and antipsychotic profile in mice and rats' see the whole document</p> <p style="text-align: center;">-----</p>	1-10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 92/ 04968

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 9-10 refers to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds
2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see annex.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

In view of the extremely large number of compounds falling under claim 1 and 2, and of the absence of any sensible support for these claims in the description, the Search division considers that it is not economically reasonable to draw a search report covering the entire subject matter of claims 1,2 and dependant claims 8 to 10.

The search report has therefore been limited to claims 3 to 7, to claims 8- 10 as far as they are dependent from claims 3 to 7 and includes all the real examples given in the description.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9204968
SA 61818

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 07/10/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0333071	20-09-89	AU-A- 3108389 JP-A- 1316399	14-09-89 21-12-89
US-A-4425269	10-01-84	None	